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☐ **1: NF-kappaB inhibitor alpha [Substance Name]**

amino acid sequence given in first source; has I kappa B-like activity; found specifically inhibit the DNA-binding activity of the p50/p65 NF-kappa B complex but not that of other DNA-binding proteins; edg-3 behaves as a sphingosine-1-phosphate receptor during differentiation of HL-60 cells
Date introduced: August 7, 1991

Registry Number: 139874-52-5

Heading Mapped to:
- I-kappa B Proteins

Entry Terms:
- I kappa B-alpha protein
- IkappaB-alpha
- IkappaBalpha
- MAD-3 protein
- MAD3 inhibitor
- major histocompatibility complex enhancer-binding protein MAD3
- p40 protein (IkappaB-alpha)

Previous Indexing:
- DNA-Binding Proteins (1999-2002)

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☐ **1: beta-Transducin Repeat-Containing Proteins**

A family of F-box domain proteins that contain sequences that are homologo to the beta subunit of transducin (BETA-TRANSDUCIN). They play an important role in the protein degradation pathway by becoming components SKP CULLIN F-BOX PROTEIN LIGASES, which selectively act on a subs proteins including beta-catenin and IkappaBbeta.
Year introduced: 2004

Subheadings: This list includes those paired at least once with this heading ir MEDLINE and may not reflect current rules for allowable combinations.

☐ analysis ☐ antagonists and inhibitors ☐ biosynthesis ☐ chemistry
☐ deficiency ☐ genetics ☐ metabolism ☐ pharmacology ☐ physiology

☐ Restrict Search to Major Topic headings only
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Entry Terms:

- Repeat-Containing Proteins, beta-Transducin
- beta Transducin Repeat Containing Proteins
- beta-TrCP
- beta TrCP
- betaTrCP
- beta-Transducin Repeat-Containing Protein
- Protein, beta-Transducin Repeat-Containing
- Repeat-Containing Protein, beta-Transducin
- beta Transducin Repeat Containing Protein

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F-Box Proteins
beta-Transducin Repeat-Containing Proteins

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ClinicalTrials.gov
PubMed Central

- If making selections (e.g., Subheadings, etc.), use the Send to Search Box fea to see PubMed records with those specifications.
- Select PubMed under the Links menu to retrieve all records for the MeSH Te
- Select NLM MeSH Browser under the Links menu for additional informatio

☐ **1: F-Box Proteins**

A family of proteins that share the F-BOX MOTIF and are involved in protei protein interactions. They play an important role in process of protein ubiqui by associating with a variety of substrates and then associating into SCF UBIQUITIN LIGASE complexes. They are held in the ubiquitin-ligase comp via binding to SKP DOMAIN PROTEINS.
Year introduced: 2004

Subheadings: This list includes those paired at least once with this heading ir MEDLINE and may not reflect current rules for allowable combinations.

☐ analysis ☐ antagonists and inhibitors ☐ biosynthesis ☐ chemistry
☐ classification ☐ genetics ☐ immunology ☐ isolation and purification
☐ metabolism ☐ physiology

☐ Restrict Search to Major Topic headings only
☐ Do Not Explode this term (i.e., do not include MeSH terms found below t term in the MeSH tree).

Entry Terms:

- F Box Proteins
- F-Box Protein Family
- F Box Protein Family
- Protein Family, F-Box
- F-Box Domain Protein
- Domain Protein, F-Box
- F Box Domain Protein
- Protein, F-Box Domain

See Also:

- F-Box Motifs

All MeSH Categories
Chemicals and Drugs Category
Amino Acids, Peptides, and Proteins
Proteins
Carrier Proteins
F-Box Proteins
beta-Transducin Repeat-Containi Proteins

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EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S1	2	"6720181".pn.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2006/07/27 10:30
S2	1	yaron.in. and lavon.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2006/07/26 12:12
S3	2	"5861048".pn.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2006/07/27 10:36
S4	2	"6268182".pn.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2006/07/27 10:38
S5	2	"7033800".pn.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2006/07/27 13:01
S7	1	"6593304".pn.	USPAT	OR	OFF	2006/07/27 14:07
S8	0	"199623069".pn.	USPAT	OR	OFF	2006/07/27 14:07
S9	0	"9623069".pn.	USPAT	OR	OFF	2006/07/27 14:07
S10	0	"9623069"	USPAT	OR	OFF	2006/07/27 14:08
S11	2	"9623069"	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2006/07/27 14:43
S12	2	"6812339".pn.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2006/07/27 15:25
S13	2	"6974688".pn.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2006/07/27 15:25
S14	704	chiaur.in. or pagano.in. or latres.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2006/08/04 10:40
S15	2	S14 and ubiquitin	USPAT	OR	OFF	2006/08/04 10:42
S16	1	S14 and fbp1	USPAT	OR	OFF	2006/08/04 10:42

EAST Search History

S17	704	chiaur.in. or pagano.in. or latres.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2006/08/04 10:42
S18	19	S17 and (ubiquitin or fbp1)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2006/08/04 10:48
S19	5	fbp1 and ikappa$	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2006/08/04 10:50
S20	3	fbp1 same ikappa$	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2006/08/04 10:50

Search Strategy for 10/652,928

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     (FILE 'HOME' ENTERED AT 12:03:32 ON 04 AUG 2006)

     FILE 'REGISTRY' ENTERED AT 12:03:39 ON 04 AUG 2006
                E "FBP1"/CN 25
                E "F-BOX PROTEIN"/CN 25
L1            2 S E16
                E "F-BOX PROTEIN"/CN 25
                E "BETA-TRCP2"/CN 25
L2            1 S E2
                E "IKAPPABALPHA"/CN 25
                E "IKAPPAB"/CN 25
                E "IKBA"/CN 25
                E "I KAPPA"/CN 25
                E "I KAPPA B-ALPHA"/CN 25
                E "MAD-3"/CN 25
L3            1 S E4

     FILE 'MEDLINE, AGRICOLA, CAPLUS, BIOSIS, EMBASE, WPIDS' ENTERED AT
     12:09:56 ON 04 AUG 2006
L4            0 S L1 AND L2 AND L3
L5        10193 S (IKAPPAB? OR MAD-3 OR MAD3)
L6          106 S L5 AND (FBP1 OR F-BOX)
L7           60 S L5 AND (BETA-TRANSDUCIN OR (BETA (W) TRANSDUCIN))
L8           60 S L5 AND (BETA-TRANSDUCIN OR (BETA (W) TRANSDUCIN) OR BTRCP?)
L9           60 S L7 AND L8
L10          37 S L6 AND L8
L11          30 DUP REM L10 (7 DUPLICATES REMOVED)

=>
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=> d 1- ibib abs
YOU HAVE REQUESTED DATA FROM 30 ANSWERS - CONTINUE? Y/(N):y

L11 ANSWER 1 OF 30 MEDLINE on STN
ACCESSION NUMBER: 2006364461 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16778892
TITLE: CRD-BP mediates stabilization of betaTrCP1 and c-myc mRNA in response to beta-catenin signalling.
AUTHOR: Noubissi Felicite K; Elcheva Irina; Bhatia Neehar; Shakoori Abbas; Ougolkov Andrei; Liu Jianghuai; Minamoto Toshinari; Ross Jeff; Fuchs Serge Y; Spiegelman Vladimir S
CORPORATE SOURCE: Department of Dermatology, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin 53706, USA.
SOURCE: Nature, (2006 Jun 15) Vol. 441, No. 7095, pp. 898-901. Journal code: 0410462. E-ISSN: 1476-4687.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200607
ENTRY DATE: Entered STN: 17 Jun 2006
Last Updated on STN: 19 Jul 2006
Entered Medline: 18 Jul 2006

AB Although constitutive activation of beta-catenin/Tcf signalling is implicated in the development of human cancers, the mechanisms by which the beta-catenin/Tcf pathway promotes tumorigenesis are incompletely understood. Messenger RNA turnover has a major function in regulating gene expression and is responsive to developmental and environmental signals. mRNA decay rates are dictated by cis-acting elements within the mRNA and by trans-acting factors, such as RNA-binding proteins (reviewed in refs 2, 3). Here we show that beta-catenin stabilizes the mRNA encoding the F-box protein betaTrCP1, and identify the RNA-binding protein CRD-BP (coding region determinant-binding protein) as a previously unknown target of beta-catenin/Tcf transcription factor. CRD-BP binds to the coding region of betaTrCP1 mRNA. Overexpression of CRD-BP stabilizes betaTrCP1 mRNA and elevates betaTrCP1 levels (both in cells and in vivo), resulting in the activation of the Skp1-Cullin1-F-box protein (SCF)(betaTrCP) E3 ubiquitin ligase and in accelerated turnover of its substrates including IkappaB and beta-catenin. CRD-BP is essential for the induction of both betaTrCP1 and c-Myc by beta-catenin signalling in colorectal cancer cells. High levels of CRD-BP that are found in primary human colorectal tumours exhibiting active beta-catenin/Tcf signalling implicates CRD-BP induction in the upregulation of betaTrCP1, in the activation of dimeric transcription factor NF-kappaB and in the suppression of apoptosis in these cancers.

L11 ANSWER 2 OF 30 MEDLINE on STN
ACCESSION NUMBER: 2005113165 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15743413
TITLE: The FWD1/beta-TrCP-mediated degradation pathway establishes a 'turning off switch' of a Cdc42 guanine nucleotide exchange factor, FGD1.
AUTHOR: Hayakawa Makio; Kitagawa Hideo; Miyazawa Keiji; Kitagawa Masatoshi; Kikugawa Kiyomi
CORPORATE SOURCE: School of Pharmacy, Tokyo University of Pharmacy and Life Science, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan.. hayakawa@ps.toyaku.ac.jp
SOURCE: Genes to cells : devoted to molecular & cellular mechanisms, (2005 Mar) Vol. 10, No. 3, pp. 241-51. Journal code: 9607379. ISSN: 1356-9597.

Search Results for 10/652,928

PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200506
ENTRY DATE: Entered STN: 4 Mar 2005
Last Updated on STN: 17 Jun 2005
Entered Medline: 16 Jun 2005

AB FWD1/beta-TrCP is the F-box protein that functions as the receptor subunit of the SCF(FWD1/beta-TrCP) ubiquitin ligase and has been shown to be responsible for the degradation of important signaling molecules such as IkappaBs and beta-catenin. Protein substrates of FWD1/beta-TrCP contain a consensus DSGPsiXS motif (where Psi represents a hydrophobic residue and X represents any amino acid). Recognition by FWD1/beta-TrCP requires phosphorylation of the conserved serines in that motif. Here we show that FGD1, a Cdc42 guanine nucleotide exchange factor (GEF), is a novel target of the SCF(FWD1/beta-TrCP) ubiquitin ligase. A mutant FGD1 protein, FGD1(SA), in which both of the critical serine residues in the DSGPsiXS motif have been replaced by alanines, does not interact with FWD1/beta-TrCP and exhibits increased stability. Morphological changes induced by wild-type FGD1 (FGD1(WT)) are reduced by the co-expression of SCF(FWD1/beta-TrCP) whereas those induced by FGD1(SA) are not affected. FGD1(SA)-expressing cells show a higher level of cell motility than FGD1(WT)-expressing cells. We present a novel 'turning off' mechanism for the inactivation of FGD1, an upstream regulator for Cdc42.

L11 ANSWER 3 OF 30 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2004021908 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14592850
TITLE: The role of [beta]-transducin repeat-containing protein ([beta]-TrCP) in the regulation of NF-[kappa]B in vascular smooth muscle cells.
AUTHOR: Wang Xiaohong; Adhikari Neeta; Li Qinglu; Guan Zhanjun; Hall Jennifer L
CORPORATE SOURCE: Lillehei Heart Institute, Division of Cardiology, Department of Medicine, University of Minnesota, Minneapolis 55455, USA.
SOURCE: Arteriosclerosis, thrombosis, and vascular biology, (2004 Jan) Vol. 24, No. 1, pp. 85-90. Electronic Publication: 2003-10-30.
Journal code: 9505803. E-ISSN: 1524-4636.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200403
ENTRY DATE: Entered STN: 15 Jan 2004
Last Updated on STN: 31 Mar 2004
Entered Medline: 30 Mar 2004

AB OBJECTIVE: Degradation of IkappaB is an essential step in nuclear factor (NF)-kappaB activation. However, the determinants regulating this process have not been defined in vascular smooth muscle cells (VSMCs). We hypothesized that the E3-ligase, beta-transducin repeat-containing protein 1 (beta-TrCP1), was a rate-determining mediator that regulates the ubiquitin-mediated degradation of IkappaBalpha (in VSMC). METHODS AND RESULTS: Upregulation of beta-TrCP1 accelerated the rate of IkappaBalpha degradation, leading to increased NF-kappaB activity. In contrast, VSMCs harboring a dominant-negative beta-TrCP1 transgene lacking the F -box domain exhibited a reduction in serum-stimulated NF-kB activity but no alteration in response to tumor necrosis factor (TNF). These findings suggest that beta-TrCP1 increases the rate of NF-kappaB

activation but is not rate-limiting in response to TNF in VSMCs. Endogenous beta-TrCP1 expression was regulated through the conserved Wnt cascade. Upregulation of Wnt1 resulted in beta-catenin-mediated activation of Tcf-4, leading to increased beta-TrCP1 expression and NF-kappaB activity. Furthermore, VSMCs harboring a Tcf-4 mutant lacking a beta-catenin binding domain exhibited a significant reduction in beta-TrCP1 expression along with abolishment of NF-kappaB activity. CONCLUSIONS: We provide the first evidence of crosstalk between the Wnt cascade and NF-kappaB signaling in VSMCs. This crosstalk is mediated through the E3-ligase, beta-TrCP1.

L11 ANSWER 4 OF 30 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2004:65561 BIOSIS
DOCUMENT NUMBER: PREV200400067344
TITLE: Interaction of Epstein-Barr virus latent membrane protein 1 with SCFHOS/beta-TrCP E3 ubiquitin ligase regulates extent of NF-kappaB activation.
AUTHOR(S): Tang, Weigang; Pavlish, Oleg A.; Spiegelman, Vladimir S.; Parkhitko, Andrey A.; Fuchs, Serge Y. [Reprint Author]
CORPORATE SOURCE: Dept. of Animal Biology, University of Pennsylvania, 3800 Spruce St., Rm. 161E, Philadelphia, PA, 19104-6046, USA sfuks@vet.upenn.edu
SOURCE: Journal of Biological Chemistry, (December 5 2003) Vol. 278, No. 49, pp. 48942-48949. print.
CODEN: JBCHA3. ISSN: 0021-9258.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 28 Jan 2004
Last Updated on STN: 28 Jan 2004
AB The Epstein-Barr virus latent membrane protein 1 (LMP1) is pivotal in the transforming activity of this virus. We found that the common LMP1-95-8 variant interacts with Homologue of Slimb (HOS), a receptor for the SCFHOS/betaTrCP ubiquitin-protein isopeptide ligase (E3) via one canonical and one cryptic HOS recognition site. These sites are mutated or deleted in the tumor-derived LMP1-Cao variant, which did not bind to HOS. Mutations within these sites on LMP1-95-8 abrogated HOS binding and increased transforming activity of LMP1. HOS did not regulate stability of LMP1-95-8 unless it was mutated to bear additional lysine residues near the cryptic motif. LMP1 proteins that could not bind to HOS exhibited an increased ability to induce IkappaB degradation and NF-kappaB-mediated transcription without further increase in activation of IkappaB kinases. Expression of LMP1-95-8 reduced the levels of endogenous HOS available to interact with phosphorylated IkappaBalpha. Degradation of IkappaBalpha and dose dependence of NF-kappaB activation by LMP1-95-8 were promoted by co-expression of HOS. Our data suggest that LMP1-95-8 is a pseudo-substrate of SCFHOS/betaTrCP E3 ubiquitin ligase and that interaction between LMP1 and HOS restricts the extent of LMP1-induced NF-kappaB signaling. We discuss the potential role of this mechanism in transforming and cytostatic effects of LMP1 variants in cells and Epstein-Barr virus-associated tumors.

L11 ANSWER 5 OF 30 MEDLINE on STN
ACCESSION NUMBER: 2003294372 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12820959
TITLE: Structure of a beta-TrCP1-Skp1-beta-catenin complex: destruction motif binding and lysine specificity of the SCF(beta-TrCP1) ubiquitin ligase.
AUTHOR: Wu Geng; Xu Guozhou; Schulman Brenda A; Jeffrey Philip D; Harper J Wade; Pavletich Nikola P
CORPORATE SOURCE: Cellular Biochemistry and Biophysics Program, Memorial Sloan-Kettering Cancer Center, New York, NY 10021, USA.

Search Results for 10/652,928

SOURCE: Molecular cell, (2003 Jun) Vol. 11, No. 6, pp. 1445-56.
Journal code: 9802571. ISSN: 1097-2765.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: PDB-1P22
ENTRY MONTH: 200308
ENTRY DATE: Entered STN: 25 Jun 2003
Last Updated on STN: 2 Aug 2003
Entered Medline: 1 Aug 2003

AB The SCF ubiquitin ligases catalyze protein ubiquitination in diverse cellular processes. SCFs bind substrates through the interchangeable F box protein subunit, with the >70 human F box proteins allowing the recognition of a wide range of substrates. The F box protein beta-TrCP1 recognizes the doubly phosphorylated DpSGphiXpS destruction motif, present in beta-catenin and IkappaB, and directs the SCF(beta-TrCP1) to ubiquitinate these proteins at specific lysines. The 3.0 A structure of a beta-TrCP1-Skp1-beta-catenin complex reveals the basis of substrate recognition by the beta-TrCP1 WD40 domain. The structure, together with the previous SCF(Skp2) structure, leads to the model of SCF catalyzing ubiquitination by increasing the effective concentration of the substrate lysine at the E2 active site. The model's prediction that the lysine-destruction motif spacing is a determinant of ubiquitination efficiency is confirmed by measuring ubiquitination rates of mutant beta-catenin peptides, solidifying the model and also providing a mechanistic basis for lysine selection.

L11 ANSWER 6 OF 30 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2003265136 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12791266
TITLE: Control of meiotic and mitotic progression by the F box protein beta-Trcp1 in vivo.
AUTHOR: Guardavaccaro Daniele; Kudo Yasusei; Boulaire Jerome; Barchi Marco; Busino Luca; Donzelli Maddalena; Margottin-Goguet Florence; Jackson Peter K; Yamasaki Lili; Pagano Michele
CORPORATE SOURCE: Department of Pathology and New York University Cancer Institute, New York University School of Medicine, New York, NY 10016, USA.
CONTRACT NUMBER: R01-CA76584 (NCI)
R01-CA79646 (NCI)
R01-GM57587 (NIGMS)
SOURCE: Developmental cell, (2003 Jun) Vol. 4, No. 6, pp. 799-812.
Journal code: 101120028. ISSN: 1534-5807.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200307
ENTRY DATE: Entered STN: 8 Jun 2003
Last Updated on STN: 26 Jul 2003
Entered Medline: 25 Jul 2003

AB SCF ubiquitin ligases, composed of three major subunits, Skp1, Cul1, and one of many F box proteins (Fbps), control the proteolysis of important cellular regulators. We have inactivated the gene encoding the Fbp beta-Trcp1 in mice. beta-Trcp1(-/-) males show reduced fertility correlating with an accumulation of methaphase I spermatocytes. beta-Trcp1(-/-) MEFs display a lengthened mitosis, centrosome overduplication, multipolar metaphase spindles, and misaligned chromosomes. Furthermore, cyclin A, cyclin B, and Emi1, an inhibitor of

the anaphase promoting complex, are stabilized in mitotic beta-Trcp1(-/-) MEFs. Indeed, we demonstrate that Emi1 is a bona fide substrate of beta-Trcp1. In contrast, stabilization of beta-catenin and IkappaBalpha, two previously reported beta-Trcp1 substrates, does not occur in the absence of beta-Trcp1 and instead requires the additional silencing of beta-Trcp2 by siRNA. Thus, beta-Trcp1 regulates the timely order of meiotic and mitotic events.

L11 ANSWER 7 OF 30 MEDLINE on STN
ACCESSION NUMBER: 2002175572 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11896578
TITLE: Mouse homologue of HOS (mHOS) is overexpressed in skin tumors and implicated in constitutive activation of NF-kappaB.
AUTHOR: Bhatia Neehar; Herter Jason R; Slaga Thomas J; Fuchs Serge Y; Spiegelman Vladimir S
CORPORATE SOURCE: AMC Cancer Research Center, Lakewood, CO 80214, USA.
CONTRACT NUMBER: CA 76262 (NCI)
CA 92900 (NCI)
SOURCE: Oncogene, (2002 Feb 28) Vol. 21, No. 10, pp. 1501-9.
Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AY038079
ENTRY MONTH: 200204
ENTRY DATE: Entered STN: 24 Mar 2002
Last Updated on STN: 19 Sep 2002
Entered Medline: 15 Apr 2002

AB NF-kappaB transcription factor is activated upon ubiquitination and subsequent proteolysis of its inhibitor IkappaB. The phosphorylation-dependent ubiquitination is mediated by SCF E3 ubiquitin ligase. In this study, we identified a novel murine F-box/WD40 repeat-containing protein, mHOS (a homologue of HOS/betaTrCP2). mHOS efficiently binds Skp1 protein (a 'core' component of SCF ubiquitin ligase), and phosphorylated IkappaB(alpha). We found that mHOS associates with SCF-ROC1 E3 ubiquitin ligase activity. We have also observed that mHOS is overexpressed in chemically-induced mouse skin tumors, and its overexpression (but not accelerated IkappaB phosphorylation) coincides with the accelerated degradation of IkappaB in vivo. The role of mHOS in the constitutive activation of NF-kappaB in skin carcinogenesis is discussed.

L11 ANSWER 8 OF 30 MEDLINE on STN
ACCESSION NUMBER: 2002118341 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11850814
TITLE: Inhibition of HOS expression and activities by Wnt pathway.
AUTHOR: Spiegelman Vladimir S; Tang Weigang; Katoh Masaru; Slaga Thomas J; Fuchs Serge Y
CORPORATE SOURCE: AMC Cancer Research Center, Lakewood, Colorado, CO 80214, USA.
CONTRACT NUMBER: CA 76262 (NCI)
CA 92900 (NCI)
SOURCE: Oncogene, (2002 Jan 24) Vol. 21, No. 5, pp. 856-60.
Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200202
ENTRY DATE: Entered STN: 21 Feb 2002

Search Results for 10/652,928

Last Updated on STN: 28 Feb 2002
Entered Medline: 27 Feb 2002

AB BetaTrCP and HOS are closely related F-box proteins, which play key roles in ubiquitination and degradation of beta-catenin and IkappaB through associating with those phosphorylated substrates and recruiting SCF E3 ubiquitin ligase. Here we report that activation of Wnt/beta-catenin signal transduction pathway elevates betaTrCP levels but inhibits expression of HOS in 293T cells. Similar disparity is likely to exist in human colorectal tumors. In the NIH3T3 cells, which express HOS, but not betaTrCP, Wnt/beta-catenin signaling leads to inhibition of HOS promoter activity and NF-kappaB-driven transcription as well as to stabilization of beta-catenin. These results indicate that expression and activities of HOS are negatively regulated by Wnt/beta-catenin pathway.

L11 ANSWER 9 OF 30 MEDLINE on STN
ACCESSION NUMBER: 2002130036 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11850407
TITLE: Pseudosubstrate regulation of the SCF(beta-TrCP) ubiquitin ligase by hnRNP-U.
AUTHOR: Davis Matti; Hatzubai Ada; Andersen Jens S; Ben-Shushan Etti; Fisher Gregory Zvi; Yaron Avraham; Bauskin Asne; Mercurio Frank; Mann Matthias; Ben-Neriah Yinon
CORPORATE SOURCE: The Lautenberg Center for Immunology, The Hebrew University-Hadassah Medical School, Jerusalem 91120, Israel.
SOURCE: Genes & development, (2002 Feb 15) Vol. 16, No. 4, pp. 439-51.
Journal code: 8711660. ISSN: 0890-9369.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200204
ENTRY DATE: Entered STN: 28 Feb 2002
Last Updated on STN: 18 Dec 2002
Entered Medline: 5 Apr 2002

AB beta-TrCP/E3RS (E3RS) is the F-box protein that functions as the receptor subunit of the SCF(beta-TrCP) ubiquitin ligase (E3). Surprisingly, although its two recognized substrates, IkappaB(alpha) and beta-catenin, are present in the cytoplasm, we have found that E3RS is located predominantly in the nucleus. Here we report the isolation of the major E3RS-associated protein, hnRNP-U, an abundant nuclear phosphoprotein. This protein occupies E3RS in a specific and stoichiometric manner, stabilizes the E3 component, and is likely responsible for its nuclear localization. hnRNP-U binding was abolished by competition with a pIkappaB(alpha) peptide, or by a specific point mutation in the E3RS WD region, indicating an E3-substrate-type interaction. However, unlike pI(kappa)Balpha, which is targeted by SCF(beta-TrCP) for degradation, the E3-bound hnRNP-U is stable and is, therefore, a pseudosubstrate. Consequently, hnRNP-U engages a highly neddylated active SCF(beta-TrCP), which dissociates in the presence of a high-affinity substrate, resulting in ubiquitination of the latter. Our study points to a novel regulatory mechanism, which secures the localization, stability, substrate binding threshold, and efficacy of a specific protein-ubiquitin ligase.

L11 ANSWER 10 OF 30 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2001423934 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11375388
TITLE: Induction of beta-transducin repeat-containing protein by JNK signaling and its role in the activation of NF-kappaB.

Search Results for 10/652,928

AUTHOR: Spiegelman V S; Stavropoulos P; Latres E; Pagano M; Ronai Z; Slaga T J; Fuchs S Y
CORPORATE SOURCE: AMC Cancer Research Center, Lakewood, Colorado 80214, Ruttenberg Cancer Center, Mount Sinai School of Medicine, New York, New York 10029, USA.
CONTRACT NUMBER: CA 76262 (NCI)
CA 92900 (NCI)
SOURCE: The Journal of biological chemistry, (2001 Jul 20) Vol. 276, No. 29, pp. 27152-8. Electronic Publication: 2001-05-24.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 27 Aug 2001
Last Updated on STN: 5 Jan 2003
Entered Medline: 23 Aug 2001

AB Activation of Jun N-kinase (JNK) and NF-kappaB transcription factor are the hallmarks of cellular response to stress. Phosphorylation of NF-kappaB inhibitor (IkappaB) by respective stress-inducible kinases (IKK) is a key event in NF-kappaB activation. beta-TrCP F -box protein mediates ubiquitination of phosphorylated IkappaB via recruitment of SCF(beta-TrCP)-Roc1 E3 ubiquitin ligase complex. Subsequent proteasome-dependent degradation of IkappaB results in activation of the NF-kappaB pathway. We found that a variety of cellular stress stimuli induce an increase in the steady state levels of beta-TrCP mRNA and protein levels in human cells. Activation of stress-activated protein kinases JNK (and, to a lesser extent, p38) by forced expression of constitutively active mutants of JNKK2 and MKK6 (but not MEK1 or IKKbeta) also leads to accumulation of beta-TrCP. Transcription of the beta-TrCP gene is not required for JNK-mediated induction of beta-TrCP. A synergistic effect of stimulation of IKK and JNK on the transcriptional activity of NF-kappaB was observed. The mechanisms of beta-TrCP induction via stress and its role in NF-kappaB activation are discussed.

L11 ANSWER 11 OF 30 MEDLINE on STN
ACCESSION NUMBER: 2001341523 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11278695
TITLE: The human immunodeficiency virus type 1 Vpu protein inhibits NF-kappa B activation by interfering with beta TrCP-mediated degradation of Ikappa B.
AUTHOR: Bour S; Perrin C; Akari H; Strebel K
CORPORATE SOURCE: Laboratory of Molecular Microbiology, NIAID, National Institutes of Health, Bethesda, Maryland 20892-0460, USA.
SOURCE: The Journal of biological chemistry, (2001 May 11) Vol. 276, No. 19, pp. 15920-8. Electronic Publication: 2001-02-16.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 18 Jun 2001
Last Updated on STN: 5 Jan 2003
Entered Medline: 14 Jun 2001

AB The human immunodeficiency virus type 1 (HIV-1) Vpu protein binds to the CD4 receptor and induces its degradation by cytosolic proteasomes. This process involves the recruitment of human betaTrCP (TrCP), a key member of

the SkpI-Cdc53-F-box E3 ubiquitin ligase complex that specifically interacts with phosphorylated Vpu molecules. Interestingly, Vpu itself, unlike other TrCP-interacting proteins, is not targeted for degradation by proteasomes. We now report that, by virtue of its affinity for TrCP and resistance to degradation, Vpu, but not a phosphorylation mutant unable to interact with TrCP, has a dominant negative effect on TrCP function. As a consequence, expression of Vpu in HIV-infected T cells or in HeLa cells inhibited TNF-alpha-induced degradation of IkappaB-alpha. Vpu did not inhibit TNF-alpha-mediated activation of the IkappaB kinase but instead interfered with the subsequent TrCP-dependent degradation of phosphorylated IkappaB-alpha. This resulted in a pronounced reduction of NF-kappaB activity. We also observed that in cells producing Vpu-defective virus, NF-kappaB activity was significantly increased even in the absence of cytokine stimulation. However, in the presence of Vpu, this HIV-mediated NF-kappaB activation was markedly reduced. These results suggest that Vpu modulates both virus- and cytokine-induced activation of NF-kappaB in HIV-1-infected cells.

L11 ANSWER 12 OF 30 MEDLINE on STN
ACCESSION NUMBER: 2001215366 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11238952
TITLE: ATF4 degradation relies on a phosphorylation-dependent interaction with the SCF(betaTrCP) ubiquitin ligase.
AUTHOR: Lassot I; Segeral E; Berlioz-Torrent C; Durand H; Groussin L; Hai T; Benarous R; Margottin-Goguet F
CORPORATE SOURCE: INSERM Unite 529, Interactions Moleculaires Hote-pathogene, 75014 Paris, France.
SOURCE: Molecular and cellular biology, (2001 Mar) Vol. 21, No. 6, pp. 2192-202.
Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 25 Apr 2001
Last Updated on STN: 25 Apr 2001
Entered Medline: 19 Apr 2001

AB The ubiquitin-proteasome pathway regulates gene expression through protein degradation. Here we show that the F-box protein betaTrCP, the receptor component of the SCF E3 ubiquitin ligase responsible for IkappaBalpha and beta-catenin degradation, is colocalized in the nucleus with ATF4, a member of the ATF-CREB bZIP family of transcription factors, and controls its stability. Association between the two proteins depends on ATF4 phosphorylation and on ATF4 serine residue 219 present in the context of DSGXXXS, which is similar but not identical to the motif found in other substrates of betaTrCP. ATF4 ubiquitination in HeLa cells is enhanced in the presence of betaTrCP. The F-box-deleted betaTrCP protein behaves as a negative transdominant mutant that inhibits ATF4 ubiquitination and degradation and, subsequently, enhances its activity in cyclic AMP-mediated transcription. ATF4 represents a novel substrate for the SCF(betaTrCP) complex, which is the first mammalian E3 ubiquitin ligase identified so far for the control of the degradation of a bZIP transcription factor.

L11 ANSWER 13 OF 30 MEDLINE on STN
ACCESSION NUMBER: 2001644244 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11696595
TITLE: The human immunodeficiency virus type 1 accessory protein Vpu induces apoptosis by suppressing the nuclear factor kappaB-dependent expression of antiapoptotic factors.

Search Results for 10/652,928

AUTHOR: Akari H; Bour S; Kao S; Adachi A; Strebel K
CORPORATE SOURCE: Laboratory of Molecular Microbiology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892, USA.
SOURCE: The Journal of experimental medicine, (2001 Nov 5) Vol. 194, No. 9, pp. 1299-311.
Journal code: 2985109R. ISSN: 0022-1007.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 7 Nov 2001
Last Updated on STN: 23 Jan 2002
Entered Medline: 18 Dec 2001

AB Human immunodeficiency virus (HIV) type 1 Vpu is an integral membrane protein with a unique affinity for betaTrCP (TrCP), a key member of the SkpI-Cullin-F-box E3 ubiquitin ligase complex that is involved in the regulated degradation of cellular proteins, including IkappaB. Remarkably, Vpu is resistant to TrCP-mediated degradation and competitively inhibits TrCP-dependent degradation of IkappaB, resulting in the suppression of nuclear factor (NF)-kappaB activity in Vpu-expressing cells. We now report that Vpu, through its interaction with TrCP, potently contributes to the induction of apoptosis in HIV-infected T cells. Vpu-induced apoptosis is specific and independent of other viral proteins. Mutation of a TrCP-binding motif in Vpu abolishes its apoptogenic property, demonstrating a close correlation between this property of Vpu and its ability to inhibit NF-kappaB activity. The involvement of NF-kappaB in Vpu-induced apoptosis is further supported by the finding that the levels of antiapoptotic factors Bcl-xL, A1/Bfl-1, and TNF receptor-associated factor (TRAF)1, all of which are expressed in an NF-kappaB-dependent manner, are reduced and, at the same time, levels of active caspase-3 are elevated. Thus, Vpu induces apoptosis through activation of the caspase pathway by way of inhibiting the NF-kappaB-dependent expression of antiapoptotic genes.

L11 ANSWER 14 OF 30 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:401972 CAPLUS
DOCUMENT NUMBER: 133:55316
TITLE: Human E3 ubiquitin ligase and βTrCP and methods for modulating ubiquitination of phospho-IκB and activation of NF-κb and disease treatment
INVENTOR(S): Manning, Anthony M.; Mercurio, Frank; Amit, Sharon; Ben-Neriah, Yinon; Davis, Matti; Hatzubai, Ada; Lavon, Iris; Yaron, Avraham
PATENT ASSIGNEE(S): Signal Pharmaceuticals, Inc., USA; Yissum Research Development Company of the Hebrew University of Jerusalem
SOURCE: PCT Int. Appl., 77 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000034447	A2	20000615	WO 1999-US29371	19991210
WO 2000034447	A3	20001109		
WO 2000034447	C2	20020829		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL,

IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2354153	AA	20000615	CA 1999-2354153	19991209
EP 1135504	A2	20010926	EP 1999-966122	19991209
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
AU 779893	B2	20050217	AU 2000-21740	19991209
US 2003166587	A1	20030904	US 2001-832161	20010409
US 6656713	B2	20031202		
US 2004203098	A1	20041014	US 2003-665715	20030919
AU 2004240212	A1	20050210	AU 2004-240212	20041220
PRIORITY APPLN. INFO.:			US 1998-210060 A	19981210
			WO 1999-US29371 W	19991210
			US 2001-832161 A3	20010409

AB Compns. and methods for modulating the activation of nuclear factor NF-κB are provided. The compns. comprise one or more agents that modulate ubiquitination of phosphorylated IκBα and/or IκBβ. Such compns. may be used for treating diseases associated with NF-κB activation, such as inflammatory diseases, autoimmune diseases, cancer, and viral infections. Modulating agents include human E3 ubiquitin ligases, antibodies thereto and variants thereof, as well as related proteins such as βTrCP. Thus, the invention is based on the identification and characterization of a human E3 ubiquitin ligase that recognizes phosphorylated and NF-κB-associated IκB. The E3 ubiquitin ligase and subfragments thereof may be used to modulate NF-κB activity.

L11 ANSWER 15 OF 30 MEDLINE on STN

ACCESSION NUMBER:	2000112860 MEDLINE
DOCUMENT NUMBER:	PubMed ID: 10644755
TITLE:	Homodimer of two F-box proteins betaTrCP1 or betaTrCP2 binds to IkappaBalpha for signal-dependent ubiquitination.
AUTHOR:	Suzuki H; Chiba T; Suzuki T; Fujita T; Ikenoue T; Omata M; Furuichi K; Shikama H; Tanaka K
CORPORATE SOURCE:	Institute for Drug Discovery Research, Yamanouchi Pharmaceutical Company Ltd., 21 Miyukigaoka, Tsukuba-shi, Ibaraki, 305-8585, Japan.
SOURCE:	The Journal of biological chemistry, (2000 Jan 28) Vol. 275, No. 4, pp. 2877-84. Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY:	United States
DOCUMENT TYPE:	Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:	English
FILE SEGMENT:	Priority Journals
ENTRY MONTH:	200002
ENTRY DATE:	Entered STN: 14 Mar 2000 Last Updated on STN: 19 Sep 2002 Entered Medline: 29 Feb 2000

AB We found previously that overexpression of an F-box protein betaTrCP1 and the structurally related betaTrCP2 augments ubiquitination of phosphorylated IkappaBalpha (pIkappaBalpha) induced by tumor necrosis factor-alpha (TNF-alpha), but the relationship of the two homologous betaTrCP proteins remains unknown. Herein we reveal that deletion mutants of betaTrCP1 and betaTrCP2 lacking the F-box domain suppressed ubiquitination and destruction of pIkappaBalpha as well as transcriptional activation of NF-kappaB. The ectopically expressed betaTrCP1 and betaTrCP2 formed both homodimer and

heterodimer complexes without displaying the trimer complex. Dimerization of betaTrCP1 and/or betaTrCP2 takes place at their conserved NH(2)-terminal regions, termed a "D-domain" (for dimerization domain), located upstream of the F-box domain. The D-domain was necessary and sufficient for the dimer formation. Intriguingly, the betaTrCP homodimer, but not the heterodimer, was selectively recruited to pIkappaBalpha induced by TNF-alpha. These results indicate that not only betaTrCP1 but also betaTrCP2 participates in the ubiquitination-dependent destruction of IkappaBalpha by forming SCF(betaTrCP1-betaTrCP1) and SCF(betaTrCP2-betaTrCP2) ubiquitin-ligase complexes.

L11 ANSWER 16 OF 30 MEDLINE on STN
ACCESSION NUMBER: 2000180061 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10713156
TITLE: Nedd8 modification of cul-1 activates SCF(beta(TrCP))-dependent ubiquitination of IkappaBalpha.
AUTHOR: Read M A; Brownell J E; Gladysheva T B; Hottelet M; Parent L A; Coggins M B; Pierce J W; Podust V N; Luo R S; Chau V; Palombella V J
CORPORATE SOURCE: LeukoSite, Inc., Cambridge, Massachusetts 02139, USA.. mread@mpi.com
CONTRACT NUMBER: GM53136 (NIGMS)
SOURCE: Molecular and cellular biology, (2000 Apr) Vol. 20, No. 7, pp. 2326-33.
Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 13 Apr 2000
Last Updated on STN: 13 Apr 2000
Entered Medline: 3 Apr 2000

AB Regulation of NF-kappaB occurs through phosphorylation-dependent ubiquitination of IkappaBalpha, which is degraded by the 26S proteasome. Recent studies have shown that ubiquitination of IkappaBalpha is carried out by a ubiquitin-ligase enzyme complex called SCF(beta(TrCP)). Here we show that Nedd8 modification of the Cul-1 component of SCF(beta(TrCP)) is important for function of SCF(beta(TrCP)) in ubiquitination of IkappaBalpha. In cells, Nedd8-conjugated Cul-1 was complexed with two substrates of SCF(beta(TrCP)), phosphorylated IkappaBalpha and beta-catenin, indicating that Nedd8-Cul-1 conjugates are part of SCF(beta(TrCP)) in vivo. Although only a minute fraction of total cellular Cul-1 is modified by Nedd8, the Cul-1 associated with ectopically expressed betaTrCP was highly enriched for the Nedd8-conjugated form. Moreover, optimal ubiquitination of IkappaBalpha required Nedd8 and the Nedd8-conjugating enzyme, Ubc12. The site of Nedd8 ligation to Cul-1 is essential, as SCF(beta(TrCP)) containing a K720R mutant of Cul-1 only weakly supported IkappaBalpha ubiquitination compared to SCF(beta(TrCP)) containing WT Cul-1, suggesting that the Nedd8 ligation of Cul-1 affects the ubiquitination activity of SCF(beta(TrCP)). These observations provide a functional link between the highly related ubiquitin and Nedd8 pathways of protein modification and show how they operate together to selectively target the signal-dependent degradation of IkappaBalpha.

L11 ANSWER 17 OF 30 MEDLINE on STN
ACCESSION NUMBER: 2000115883 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10648623
TITLE: The SCF(HOS/beta-TRCP)-ROC1 E3 ubiquitin ligase utilizes two distinct domains within CUL1 for substrate targeting and ubiquitin ligation.

Search Results for 10/652,928

AUTHOR: Wu K; Fuchs S Y; Chen A; Tan P; Gomez C; Ronai Z; Pan Z Q
CORPORATE SOURCE: Derald H. Ruttenberg Cancer Center, The Mount Sinai School of Medicine, New York, New York 10029-6574, USA.
CONTRACT NUMBER: CA78419 (NCI)
GM55059 (NIGMS)
SOURCE: Molecular and cellular biology, (2000 Feb) Vol. 20, No. 4, pp. 1382-93.
Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 29 Feb 2000
Last Updated on STN: 19 Sep 2002
Entered Medline: 15 Feb 2000

AB We describe a purified ubiquitination system capable of rapidly catalyzing the covalent linkage of polyubiquitin chains onto a model substrate, phosphorylated IkappaBalpha. The initial ubiquitin transfer and subsequent polymerization steps of this reaction require the coordinated action of Cdc34 and the SCF(HOS/beta-TRCP)-ROC1 E3 ligase complex, comprised of four subunits (Skp1, cullin 1 [CUL1], HOS/beta-TRCP, and ROC1). Deletion analysis reveals that the N terminus of CUL1 is both necessary and sufficient for binding Skp1 but is devoid of ROC1-binding activity and, hence, is inactive in catalyzing ubiquitin ligation. Consistent with this, introduction of the N-terminal CUL1 polypeptide into cells blocks the tumor necrosis factor alpha-induced and SCF-mediated degradation of IkappaB by forming catalytically inactive complexes lacking ROC1. In contrast, the C terminus of CUL1 alone interacts with ROC1 through a region containing the cullin consensus domain, to form a complex fully active in supporting ubiquitin polymerization. These results suggest the mode of action of SCF-ROC1, where CUL1 serves as a dual-function molecule that recruits an F -box protein for substrate targeting through Skp1 at its N terminus, while the C terminus of CUL1 binds ROC1 to assemble a core ubiquitin ligase.

L11 ANSWER 18 OF 30 MEDLINE on STN
ACCESSION NUMBER: 2000160458 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10694485
TITLE: Molecular cloning and genomic structure of the betaTRCP2 gene on chromosome 5q35.1.
AUTHOR: Koike J; Sagara N; Kirikoshi H; Takagi A; Miwa T; Hirai M; Katoh M
CORPORATE SOURCE: Genetics Division, National Cancer Center Research Institute, Tsukiji 5-chome, Chuo-ku, Tokyo, 104-0045, Japan.
SOURCE: Biochemical and biophysical research communications, (2000 Mar 5) Vol. 269, No. 1, pp. 103-9.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AB033279; GENBANK-AB033280; GENBANK-AB033281
ENTRY MONTH: 200003
ENTRY DATE: Entered STN: 13 Apr 2000
Last Updated on STN: 13 Apr 2000
Entered Medline: 31 Mar 2000

AB Beta-catenin, IkappaBalpha, and HIV Vpu are recruited to the ubiquitin-proteasome degradation pathway by betaTRCP, one of the components of the ubiquitin ligase complex. betaTRCP2, a related gene of

Search Results for 10/652,928

betaTRCP, was cloned and characterized. Three isoforms, betaTRCP2A, betaTRCP2B, and betaTRCP2C, were identified. All of these betaTRCP2 isoforms consist of an F-box and seven WD repeats.
Human betaTRCP2A shows 86% total amino acid identity with human betaTRCP. betaTRCP2 mRNA of 4.5 kb in size was detected almost ubiquitously. Sequence analyses on betaTRCP2 genomic clones revealed that the betaTRCP2 gene consists of at least 14 exons. Exons 1 and 4-14 are shared among all betaTRCP2 isoforms. betaTRCP2A of 508 amino acids lacks exons 2 and 3, betaTRCP2B of 529 amino acids contains exon 3, and betaTRCP2C of 542 amino acids contains exon 2. These results indicate that three betaTRCP2 isoforms are transcribed due to alternative splicing. The betaTRCP2 gene has been mapped to human chromosome 5q35.1 by fluorescence in situ hybridization.

L11 ANSWER 19 OF 30 WPIDS
ACCESSION NUMBER: 1999-469329 [39] WPIDS
DOC. NO. NON-CPI: N1999-350425
DOC. NO. CPI: C1999-137771
TITLE: New human beta-transducin repeat containing protein and its fragments useful as, or to screen for, antiviral, antitumor, anti-inflammatory and anti-Alzheimer agents.
DERWENT CLASS: B04 D16 P14
INVENTOR(S): ARENZANA SEISDEDOS, F; BENAROUS, R; CONCORDET, J; DURAND, H; KROLL, M; MARGOTTIN, F
PATENT ASSIGNEE(S): (INRM) INSERM INST NAT SANTE & RECH MEDICALE; (INRM) INST NAT SANTE & RECH MEDICALE; (INSP) INST PASTEUR
COUNTRY COUNT: 85
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9938969	A1	19990805	(199939)*	FR	70
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW					
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW					
FR 2774377	A1	19990806	(199939)		
FR 2774378	A1	19990806	(199939)		
AU 9921694	A	19990816	(200002)		
EP 1049775	A1	20001108	(200062)	FR	
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					
JP 2002501746	W	20020122	(200211)		80
US 6730486	B1	20040504	(200430)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9938969	A1	WO 1999-FR196	19990129
FR 2774377	A1	FR 1998-1100	19980130
FR 2774378	A1	FR 1998-15545	19981209
AU 9921694	A	AU 1999-21694	19990129
EP 1049775	A1	EP 1999-901671	19990129
		WO 1999-FR196	19990129
JP 2002501746	W	WO 1999-FR196	19990129
		JP 2000-529429	19990129
US 6730486	B1	WO 1999-FR196	19990129
		US 2000-601168	20000728

Search Results for 10/652,928

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 9921694	A Based on	WO 9938969
EP 1049775	A1 Based on	WO 9938969
JP 2002501746	W Based on	WO 9938969
US 6730486	B1 Based on	WO 9938969

PRIORITY APPLN. INFO: FR 1998-15545 19981209; FR 1998-1100 19980130

AN 1999-469329 [39] WPIDS

AB WO 9938969 A UPAB: 19990928

NOVELTY - Human protein beta TrcP (I; beta-transducin repeats containing protein), for directing proteins to the proteosome degradation pathways, has a 569 amino acid (aa) sequence (2), given in the specification.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) peptide fragments (Ia) of (I), formed by addition, deletion and/or substitution of one or more aa, and retaining ability to interact with the Vpu protein of human immune deficiency virus-1 (HIV-1), cellular proteins IkappaB or beta -catenin (bC) and/or protein Skp1p;

(2) nucleic acid (II) encoding (I) or (Ia);

(3) anti-HIV agents comprising (Ia) lacking either the F box or the WD motifs;

(4) antibodies (Ab) directed against (I) or (Ia);

(5) antisense oligonucleotides that block transcription or translation of (I) by hybridization;

(6) antitumor agents comprising (Ia) that retain both F box and WD motifs;

(7) anti-inflammatory agents comprising (Ia) that lack the F box;

(8) transgenic animals that:

(a) express the transgene for (I); or

(b) have the endogenous gene for beta TrcP inactivated;

(9) expression vectors containing (II); and

(10) microorganisms or transformed cells containing this vector and optionally also a vector that expresses one of Vpu, IkappaB, Skp1p or bC.

ACTIVITY - Antiviral; Antitumor; Anti-inflammatory; Anti-Alzheimer.

MECHANISM OF ACTION - (I) controls ubiquitinylation of phosphorylated proteins and thus their targeting to proteosomes for degradation. Depending on whether the process is inhibited or promoted, the result may be delayed breakdown of CD4 (in cases of HIV-1 infection); increased activity of IkB (and thus reduced activity of NFkappaB) and increased degradation of mutant bC in tumor cells, or increased bC survival (and reduced apoptosis) in Alzheimer patients.

USE - (I), and its active peptide fragments (Ib), or nucleic acid (II), encoding them, are used to screen for:

(a) anti-human immune deficiency virus-1 (HIV-1) agents that inhibit interaction between (I) and Vpu or Skp1p;

(b) antitumor agents that disrupt cell cycle regulation or protein degradation in human tumor cells by modulating interaction between (I) and Skp1p;

(c) anti-inflammatory agents that disrupt activation by NFkappaB, by inhibiting (I)/IkappaB interaction; and

(d) antitumor agents that can reactivate interaction of (I) with:

(i) mutant bC in tumor cells; or

(ii) with normal bC in cells that lack APC.

Fragments of (I) are also useful as anti-HIV, antitumor and

anti-inflammatory agents (optionally generated by gene therapy), particularly for treating osteo-articular inflammation or acute inflammation associated with release of tumor necrosis factor.

(I), (Ia) and (II) are also used to detect mutations in bC (for diagnosis of tumors), while (I) may be used to raise specific antibodies (Ab) that have antiviral, antitumor and anti-inflammatory activity. Antisense oligonucleotides directed against (II) can be used similarly.

Transgenic animals that express (I) or lack the equivalent endogenous protein are used to study disorders of the cell cycle and proliferation, in cases of absence or overexpression of (I) or of truncated or mutated forms of Skp1p, Vpu, IkappaB or bC.

Dwg.0/12

L11 ANSWER 20 OF 30 MEDLINE on STN
ACCESSION NUMBER: 1999445507 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10514433
TITLE: Molecular dissection of the interactions among IkappaBalpha, FWD1, and Skp1 required for ubiquitin-mediated proteolysis of IkappaBalpha.
AUTHOR: Hattori K; Hatakeyama S; Shirane M; Matsumoto M; Nakayama K
CORPORATE SOURCE: Department of Molecular Biology, Medical Institute of Bioregulation, Kyushu University, Fukuoka 812-8582, Japan.
SOURCE: The Journal of biological chemistry, (1999 Oct 15) Vol. 274, No. 42, pp. 29641-7.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199911
ENTRY DATE: Entered STN: 11 Jan 2000
Last Updated on STN: 19 Sep 2002
Entered Medline: 19 Nov 1999

AB The SCF complex containing Skp1, Cul1, and the F-box protein FWD1 (the mouse homologue of Drosophila Slimb and Xenopus beta-TrCP) functions as the ubiquitin ligase for IkappaBalpha. FWD1 associates with Skp1 through the F-box domain and also recognizes the conserved DSGXXS motif of IkappaBalpha. The structural requirements for the interactions of FWD1 with IkappaBalpha and with Skp1 have now been investigated further. The D31A mutation (but not the G33A mutation) in the DSGXXS motif of IkappaBalpha abolished the binding of IkappaBalpha to FWD1 and its subsequent ubiquitination without affecting the phosphorylation of IkappaBalpha. The IkappaBalpha mutant D31E still exhibited binding to FWD1 and underwent ubiquitination. These results suggest that, in addition to site-specific phosphorylation at Ser(32) and Ser(36), an acidic amino acid at position 31 is required for FWD1-mediated ubiquitination of IkappaBalpha. Deletion analysis of Skp1 revealed that residues 61-143 of this protein are required for binding to FWD1. On the other hand, the highly conserved residues Pro(149), Ile(160), and Leu(164) in the F-box domain of FWD1 were dispensable for binding to Skp1. Together, these data delineate the structural requirements for the interactions among IkappaBalpha, FWD1, and Skp1 that underlie substrate recognition by the SCF ubiquitin ligase complex.

L11 ANSWER 21 OF 30 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 1999445498 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10514424
TITLE: beta-TrCP mediates the signal-induced ubiquitination of IkappaBbeta.
AUTHOR: Wu C; Ghosh S

CORPORATE SOURCE: Section of Immunobiology, Department of Molecular Biophysics, Howard Hughes Medical Institute, Yale University School of Medicine, New Haven, Connecticut 06520, USA.
CONTRACT NUMBER: R01 AI33443 (NIAID)
SOURCE: The Journal of biological chemistry, (1999 Oct 15) Vol. 274, No. 42, pp. 29591-4.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199911
ENTRY DATE: Entered STN: 11 Jan 2000
Last Updated on STN: 11 Jan 2000
Entered Medline: 19 Nov 1999

AB We have examined the role of beta-TrCP (beta-transducin repeat-containing protein) in the ubiquitination and degradation of IkappaBbeta, one of the two major IkappaB isoforms in mammalian cells. We demonstrate that beta-TrCP interacts specifically with IkappaBbeta, and such interaction is dependent on prior phosphorylation of IkappaBbeta on serines 19 and 23. Interaction with beta-TrCP is also necessary for ubiquitination of IkappaBbeta upon stimulation of cells, and deletion of the F-box in beta-TrCP abolishes its ability to ubiquitinate IkappaBbeta. Therefore, these results indicate that beta-TrCP plays a critical role in the activation of NF-kappaB by assembling the ubiquitin ligase complex for both phosphorylated IkappaBalpha and IkappaBbeta.

L11 ANSWER 22 OF 30 MEDLINE on STN
ACCESSION NUMBER: 1999428479 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10497169
TITLE: Common pathway for the ubiquitination of IkappaBalpha, IkappaBbeta, and IkappaBepsilon mediated by the F-box protein FWD1.
AUTHOR: Shirane M; Hatakeyama S; Hattori K; Nakayama K; Nakayama K
CORPORATE SOURCE: Department of Molecular Biology, Medical Institute of Bioregulation, Kyushu University, Fukuoka 812-8582, Japan.
SOURCE: The Journal of biological chemistry, (1999 Oct 1) Vol. 274, No. 40, pp. 28169-74.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199911
ENTRY DATE: Entered STN: 11 Jan 2000
Last Updated on STN: 11 Jan 2000
Entered Medline: 2 Nov 1999

AB FWD1 (the mouse homolog of Drosophila Slimb and Xenopus betaTrCP, a member of the F-box- and WD40 repeat-containing family of proteins, and a component of the SCF ubiquitin ligase complex) was recently shown to interact with IkappaBalpha and thereby to promote its ubiquitination and degradation. This protein has now been shown also to bind to IkappaBbeta and IkappaBepsilon as well as to induce their ubiquitination and proteolysis. FWD1 was shown to recognize the conserved DSGPsiXS motif (where Psi represents the hydrophobic residue) present in the NH(2)-terminal regions of these three IkappaB proteins only when the component serine residues are phosphorylated. However, in contrast to IkappaBalpha and

IkappaBbeta, the recognition site in IkappaBepsilon for FWD1 is not restricted to the DSGPsiXS motif; FWD1 also interacts with other sites in the NH(2)-terminal region of IkappaBepsilon. Substitution of the critical serine residues in the NH(2)-terminal regions of IkappaBalpha, IkappaBbeta, and IkappaBepsilon with alanines also markedly reduced the extent of FWD1-mediated ubiquitination of these proteins and increased their stability. These data indicate that the three IkappaB proteins, despite their substantial structural and functional differences, all undergo ubiquitination mediated by the SCF(FWD1) complex. FWD1 may thus play an important role in NF-kappaB signal transduction through regulation of the stability of multiple IkappaB proteins.

L11 ANSWER 23 OF 30 MEDLINE on STN
ACCESSION NUMBER: 1999175170 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10075690
TITLE: Inducible degradation of IkappaBalpha by the proteasome requires interaction with the F-box protein h-betaTrCP.
AUTHOR: Kroll M; Margottin F; Kohl A; Renard P; Durand H; Concordet J P; Bachelerie F; Arenzana-Seisdedos F; Benarous R
CORPORATE SOURCE: Unite d'Immunologie Virale, Unite des arbovirus et virus des fievres hemorragiques, Institut Pasteur, 25 et 28, rue du Dr. Roux, 75724 Paris Cedex 15, France.
SOURCE: The Journal of biological chemistry, (1999 Mar 19) Vol. 274, No. 12, pp. 7941-5.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 26 Apr 1999
Last Updated on STN: 19 Sep 2002
Entered Medline: 15 Apr 1999

AB Activation of NF-kappaB transcription factors requires phosphorylation and ubiquitin-proteasome-dependent degradation of IkappaB proteins. We provide evidence that a human F-box protein, h-betaTrCP, a component of Skp1-Cullin-F-box protein (SCF) complexes, a new class of E3 ubiquitin ligases, is essential for inducible degradation of IkappaBalpha. betaTrCP associates with Ser32-Ser36 phosphorylated, but not with unmodified IkappaBalpha or Ser32-Ser36 phosphorylation-deficient mutants. Expression of a F-box-deleted betaTrCP inhibits IkappaBalpha degradation, promotes accumulation of phosphorylated Ser32-Ser36 IkappaBalpha, and prevents NF-kappaB-dependent transcription. Our findings indicate that betaTrCP is the adaptor protein required for IkappaBalpha recognition by the SCFbetaTrCP E3 complex that ubiquitinates IkappaBalpha and makes it a substrate for the proteasome.

L11 ANSWER 24 OF 30 MEDLINE on STN
ACCESSION NUMBER: 1999253645 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10321728
TITLE: HOS, a human homolog of Slimb, forms an SCF complex with Skp1 and Cullin1 and targets the phosphorylation-dependent degradation of IkappaB and beta-catenin.
AUTHOR: Fuchs S Y; Chen A; Xiong Y; Pan Z Q; Ronai Z
CORPORATE SOURCE: Derald H Ruttenberg Cancer Center, Mount Sinai School of Medicine, New York, NY 10029-6574, USA.
CONTRACT NUMBER: CA 78419 (NCI)
GM 55059 (NIGMS)

Search Results for 10/652,928

SOURCE: Oncogene, (1999 Mar 25) Vol. 18, No. 12, pp. 2039-46.
Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AB014596
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 14 Jun 1999
Last Updated on STN: 4 Mar 2003
Entered Medline: 3 Jun 1999

AB SCF E3 ubiquitin ligases mediate ubiquitination and proteasome-dependent degradation of phosphorylated substrates. We identified a human F -box/WD40 repeats protein (HOS), which is homologous to Slimb/h betaTrCP. Being a part of SCF complex with Skp1 and Cullin1, HOS specifically interacted with the phosphorylated IkappaB and beta-catenin, targeting these proteins for proteasome-dependent degradation in vivo. This targeting required Cullin1 as expression of a mutant Cullin1 abrogated the degradation of IkappaB and of beta-catenin. Mutant HOS which lacks the F-box blocked TNF alpha-induced degradation of IkappaB as well as GSK3beta-mediated degradation of beta-catenin. This mutant also inhibited NF-kappaB transactivation and increased the beta-catenin-dependent transcription activity of Tcf. These results demonstrate that SCF(HOS) E3 ubiquitin ligase regulate both NF-kappaB and beta-catenin signaling pathways.

L11 ANSWER 25 OF 30 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:295791 CAPLUS
DOCUMENT NUMBER: 131:268431
TITLE: The SCFβ-TRCP-ubiquitin ligase complex associates specifically with phosphorylated destruction motifs in IκBα and β-catenin and stimulates IκBα ubiquitination in vitro. [Erratum to document cited in CA131:1749]
AUTHOR(S): Winston, Jeffrey T.; Strack, Peter; Beer-Romero, Peggy; Chu, Claire Y.; Elledge, Stephen J.; Harper, J. Wade
CORPORATE SOURCE: Verna & Marrs McLean Department of Biochemistry, Baylor College of Medicine, Houston, TX, 77030, USA
SOURCE: Genes & Development (1999), 13(8), 1050
CODEN: GEDEEP; ISSN: 0890-9369
PUBLISHER: Cold Spring Harbor Laboratory Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Fig. 3a was misprinted; the correct figure and its legend are given.

L11 ANSWER 26 OF 30 MEDLINE on STN
ACCESSION NUMBER: 1999364506 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10437795
TITLE: A complex containing betaTrCP recruits Cdc34 to catalyse ubiquitination of IkappaBalpha.
AUTHOR: Vuillard L; Nicholson J; Hay R T
CORPORATE SOURCE: School of Biomedical Science, University of St. Andrews, Fife, UK.
SOURCE: FEBS letters, (1999 Jul 23) Vol. 455, No. 3, pp. 311-4.
Journal code: 0155157. ISSN: 0014-5793.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199908

Search Results for 10/652,928

ENTRY DATE: Entered STN: 27 Aug 1999
Last Updated on STN: 19 Sep 2002
Entered Medline: 16 Aug 1999

AB Activation of transcription factor NF-kappaB is accomplished by degradation of its inhibitor IkappaBalpha. Signal induced phosphorylation of IkappaBalpha on serine 32 and 36 targets the protein for ubiquitination on lysine 21 and 22. Here we use a phosphorylated peptide substrate representing residues 20-43 of IkappaBalpha to investigate requirements for ubiquitination of IkappaBalpha. Phosphorylation dependent polyubiquitination is carried out by a multiprotein complex containing betaTrCP, Skp1 and Cdc53 (Cull). In the presence of ubiquitin activating enzyme and the protein complex containing betaTrCP, polyubiquitination of IkappaBalpha peptide was dependent on the presence of Cdc34, while Ubc5 only stimulated mono- and di-ubiquitination.

L11 ANSWER 27 OF 30 MEDLINE on STN
ACCESSION NUMBER: 1999145465 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9990853
TITLE: Signal-induced ubiquitination of IkappaBalpha by the F-box protein Slimb/beta-TrCP.
AUTHOR: Spencer E; Jiang J; Chen Z J
CORPORATE SOURCE: Department of Molecular Biology and Oncology, University of Texas Southwestern Medical Center, Dallas, Texas 75235-9148 USA.
SOURCE: Genes & development, (1999 Feb 1) Vol. 13, No. 3, pp. 284-94.
Journal code: 8711660. ISSN: 0890-9369.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF112979
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 20 Apr 1999
Last Updated on STN: 4 Mar 2003
Entered Medline: 2 Apr 1999

AB Signal-induced phosphorylation of IkappaBalpha targets this inhibitor of NF-kappaB for ubiquitination and subsequent degradation, thus allowing NF-kappaB to enter the nucleus to turn on its target genes. We report here the identification of an IkappaB-ubiquitin (Ub) ligase complex containing the F-box/WD40-repeat protein, beta-TrCP, a vertebrate homolog of Drosophila Slimb. beta-TrCP binds to IkappaBalpha only when the latter is specifically phosphorylated by an IkappaB kinase complex. Moreover, immunopurified beta-TrCP ubiquitinates phosphorylated IkappaBalpha at specific lysines in the presence of Ub-activating (E1) and -conjugating (Ubch5) enzymes. A beta-TrCP mutant lacking the F-box inhibits the signal-induced degradation of IkappaBalpha and subsequent activation of NF-kappaB-dependent transcription. Furthermore, Drosophila embryos deficient in slimb fail to activate twist and snail, two genes known to be regulated by the NF-kappaB homolog, Dorsal. These biochemical and genetic data strongly suggest that Slimb/beta-TrCP is the specificity determinant for the signal-induced ubiquitination of IkappaBalpha.

L11 ANSWER 28 OF 30 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 1999145464 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9990852
TITLE: The SCFbeta-TRCP-ubiquitin ligase complex associates specifically with phosphorylated destruction motifs in IkappaBalpha and beta-catenin and stimulates

Search Results for 10/652,928

IkappaBalpha ubiquitination in vitro.
AUTHOR: Winston J T; Strack P; Beer-Romero P; Chu C Y; Elledge S J; Harper J W
CORPORATE SOURCE: Verna & Marrs McLean Department of Biochemistry, Baylor College of Medicine, Houston, Texas 77030 USA.
SOURCE: Genes & development, (1999 Feb 1) Vol. 13, No. 3, pp. 270-83.
Journal code: 8711660. ISSN: 0890-9369.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF110396
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 20 Apr 1999
Last Updated on STN: 19 Sep 2002
Entered Medline: 2 Apr 1999

AB Ubiquitin-mediated proteolysis has a central role in controlling the intracellular levels of several important regulatory molecules such as cyclins, CKIs, p53, and IkappaBalpha. Many diverse proinflammatory signals lead to the specific phosphorylation and subsequent ubiquitin-mediated destruction of the NF-kappaB inhibitor protein IkappaBalpha. Substrate specificity in ubiquitination reactions is, in large part, mediated by the specific association of the E3-ubiquitin ligases with their substrates. One class of E3 ligases is defined by the recently described SCF complexes, the archetype of which was first described in budding yeast and contains Skp1, Cdc53, and the F-box protein Cdc4. These complexes recognize their substrates through modular F-box proteins in a phosphorylation-dependent manner. Here we describe a biochemical dissection of a novel mammalian SCF complex, SCFbeta-TRCP, that specifically recognizes a 19-amino-acid destruction motif in IkappaBalpha (residues 21-41) in a phosphorylation-dependent manner. This SCF complex also recognizes a conserved destruction motif in beta-catenin, a protein with levels also regulated by phosphorylation-dependent ubiquitination. Endogenous IkappaBalpha-ubiquitin ligase activity cofractionates with SCFbeta-TRCP. Furthermore, recombinant SCFbeta-TRCP assembled in mammalian cells contains phospho-IkappaBalpha-specific ubiquitin ligase activity. Our results suggest that an SCFbeta-TRCP complex functions in multiple transcriptional programs by activating the NF-kappaB pathway and inhibiting the beta-catenin pathway.

L11 ANSWER 29 OF 30 MEDLINE on STN
ACCESSION NUMBER: 1999167350 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10066435
TITLE: IkappaBalpha ubiquitination is catalyzed by an SCF-like complex containing Skp1, cullin-1, and two F-box/WD40-repeat proteins, betaTrCP1 and betaTrCP2.
AUTHOR: Suzuki H; Chiba T; Kobayashi M; Takeuchi M; Suzuki T; Ichiyama A; Ikenoue T; Omata M; Furuichi K; Tanaka K
CORPORATE SOURCE: Institute for Drug Discovery Research, Yamanouchi Pharmaceutical Co., Ltd., 21 Miyukigaoka, Ibaraki, Tsukuba-shi, 305-8585, Japan.
SOURCE: Biochemical and biophysical research communications, (1999 Mar 5) Vol. 256, No. 1, pp. 127-32.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

Search Results for 10/652,928

ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 26 Apr 1999
Last Updated on STN: 19 Sep 2002
Entered Medline: 13 Apr 1999

AB Destruction of the transcriptional inhibitor IkappaB by the ubiquitin (Ub) system is required for signal-dependent activation of the multifunctional transcriptional factor NF-kappaB, but details of this ubiquitination are largely unknown. We report here that the IkappaBalpha-ubiquitin ligase (IkappaBalpha-E3) is an SCF-like complex containing Skp1, cullin-1, and two homologous F -box/WD40-repeat proteins, betaTrCP1 and betaTrCP2. Intriguingly, all these components are cooperatively recruited to bind to a phosphorylated IkappaBalpha (pIkappaBalpha) produced by tumor necrosis factor-alpha (TNF-alpha) stimulation. IkappaBalpha-E3 bound to pIkappaBalpha catalyzed in vitro ubiquitination of pIkappaBalpha in the presence of ATP, Ub, and E1-activating and E2-conjugating enzymes. Forced expression of betaTrCP1 and betaTrCP2 resulted in dramatic augmentation of the in vitro polyubiquitination activity of IkappaBalpha-E3. These results indicate that the long-sought IkappaBalpha-E3 is an SCF-like complex consisting of multiple proteins which are coordinately assembled during phosphorylation of IkappaBalpha in response to external signals.

L11 ANSWER 30 OF 30 MEDLINE on STN
ACCESSION NUMBER: 1999075339 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9859996
TITLE: Identification of the receptor component of the IkappaBalpha-ubiquitin ligase.
AUTHOR: Yaron A; Hatzubai A; Davis M; Lavon I; Amit S; Manning A M; Andersen J S; Mann M; Mercurio F; Ben-Neriah Y
CORPORATE SOURCE: The Lautenberg Center for Immunology, The Hebrew University-Hadassah Medical School, Jerusalem, Israel.
SOURCE: Nature, (1998 Dec 10) Vol. 396, No. 6711, pp. 590-4. Journal code: 0410462. ISSN: 0028-0836.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF099932; GENBANK-AF101784
ENTRY MONTH: 199901
ENTRY DATE: Entered STN: 15 Jan 1999
Last Updated on STN: 19 Sep 2002
Entered Medline: 7 Jan 1999

AB NF-kappaB, a ubiquitous, inducible transcription factor involved in immune, inflammatory, stress and developmental processes, is retained in a latent form in the cytoplasm of non-stimulated cells by inhibitory molecules, IkappaBs. Its activation is a paradigm for a signal-transduction cascade that integrates an inducible kinase and the ubiquitin-proteasome system to eliminate inhibitory regulators. Here we isolate the pIkappaBalpha-ubiquitin ligase (pIkappaBalpha-E3) that attaches ubiquitin, a small protein which marks other proteins for degradation by the proteasome system, to the phosphorylated NF-kappaB inhibitor pIkappaBalpha. Taking advantage of its high affinity to pIkappaBalpha, we isolate this ligase from HeLa cells by single-step immunoaffinity purification. Using nanoelectrospray mass spectrometry, we identify the specific component of the ligase that recognizes the pIkappaBalpha degradation motif as an F-box/WD-domain protein belonging to a recently distinguished family of beta-TrCP/Slimb proteins. This component, which we denote E3RSIkappaB (pIkappaBalpha-E3 receptor subunit), binds specifically to pIkappaBalpha and promotes its in vitro ubiquitination in the presence of two other ubiquitin-system

enzymes, E1 and UBC5C, one of many known E2 enzymes. An F-box-deletion mutant of E3RS(IkappaB), which tightly binds pIkappaBalpha but does not support its ubiquitination, acts in vivo as a dominant-negative molecule, inhibiting the degradation of pIkappaBalpha and consequently NF-kappaB activation. E3RS(IkappaB) represents a family of receptor proteins that are core components of a class of ubiquitin ligases. When these receptor components recognize their specific ligand, which is a conserved, phosphorylation-based sequence motif, they target regulatory proteins containing this motif for proteasomal degradation.